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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,632	04/07/1999	PETER MICHAEL WATERHOUSE	021565-060	6526

21839 7590 12/08/2009

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ALEXANDRIA, VA 22313-1404

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
12/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	09/287,632	WATERHOUSE ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *1-10,12,40,43,44,46,50,98,99 and 111-114* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,26,42,53,54,56,58,63-69,100-103,109 and 115-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-22-09,6-10-09,6-23-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-10,12,22,26,40,42-44,46,50,53,54,56,58,63-69,98-103,109 and 111-122.

DETAILED ACTION

This Office action is in response to the communication filed 11-5-09.

Claims 1-10, 12, 22, 26, 40, 42-44, 46, 50, 53, 54, 56, 58, 63-69, 98-103, 109, 111-122 are pending in the instant application. Claims 1-10, 12, 40, 43, 44, 46, 50, 98, 99, 111-114 are withdrawn as being drawn to a non-elected invention, and claims 22, 26, 42, 53, 54, 56, 58, 63-69, 100-103, 109, 115-122 have been examined on their merits as set forth below.

The declarations under 37 CFR 1.132 filed 3-19-09 and in previous filings by Applicant are insufficient to overcome the rejections based upon 35 U.S.C. 112, first paragraph and 35 U.S.C. 103(a) as set forth in the last Office action and for the reasons set forth below.

Election/Restrictions

This application contains claims 1-10, 12, 40, 43, 44, 46, 50, 98, 99, 111-114 drawn to an invention nonelected with traverse in the reply filed on 12-3-04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 100-103, 109, 115-122 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 9-19-08, 5-11-09, and for the reasons set forth below.

Applicant's arguments filed 11-5-09, and the declarations filed 5-7-08 and 3-19-09 have been fully considered but they are not fully persuasive. Applicant argues that a person of ordinary skill in the art would have recognized from the application as filed that the inventors were in possession of the invention as currently claimed.

The claims are drawn to any plants and any eukaryotic cells comprising any nucleic acid of interest which is capable of being phenotypically expressed, and comprising any chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a DNA region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 20, 50, 100, or 550 consecutive nucleotides having 100% sequence identity with at least 20, 50, 100, or 550 consecutive nucleotides of any nucleic acid of interest, and which antisense sequence includes at least 20, 50, 100, or 550 consecutive nucleotides having 100% sequence

identity with said at least 20, 50, 100, or 550 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises an intron.

The initial disclosure teaches fully complementary pair constructs for reducing the phenotypic expression of a transgenic Gus gene (of approximately 1580 base pairs), and complementary pair constructs for reducing the phenotypic expression of the Δ12 desaturase target gene in *Arabidopsis* (of approximately 620 base pairs) which complementary pair constructs additionally comprise the pyruvate orthophosphate dikinase 2 intron 2 from *Flaveria trinervia* (SEQ ID NO. 7) in forward or reverse orientation. The declarations filed 5-1-08 teach three expression constructs, one which comprises a double stranded hairpin of at least 750 base pairs that comprises a sequence fully complementary to and targets the potato virus Y gene, and which expression construct further comprises intron 2 of pdkA, which was transformed into *Agrobacterium*, and a second and third double stranded construct of at least 558 base pairs that targets and is fully complementary to the target GUS gene, and optionally comprise the Ubi-1 intron, which nucleic acid constructs were transformed into rice calli.

The examples provided in the declarations and in the instant disclosure are not representative of the very broad genus of compounds, eukaryotic cells, and plants claimed, which encompass any plant and any eukaryotic cell comprising any nucleic acid capable of expressing a phenotype, and comprising chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising any DNA region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with

a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 20, 50, 100, or 550 consecutive nucleotides having 100% sequence identity with at least 20, 50, 100, or 550 consecutive nucleotides of any nucleic acid of interest, and which antisense sequence includes at least 20, 50, 100, or 550 consecutive nucleotides having 100% sequence identity with said at least 20, 50, 100, or 550 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises an intron.

Applicants, by providing the examples described above, were not in possession of the broad array of compounds, cells, or plants claimed, comprising any nucleic acid capable of expressing a phenotype, and further comprising a hairpin construct fully complementary and targeting any nucleic acid capable of expressing a phenotype, at the time of filing. The genus of plants, eukaryotic cells and chimeric constructs is expansive, and adequate representation of species encompassing this myriad of plants, eukaryotic cells and chimeric constructs has not been made, either prior to December 23, 1997, or at the time of filing. See also, *e.g.* page 3 of the declaration of Marc De Block submitted on 6-8-07, paragraph 14, reporting hairpin constructs that failed to provide a predictable phenotype of differences in flowering in oilseed rape, and depended on the insertion of a particular intron in a particular expression construct. Furthermore, the declarations and experimental examples provided in the initial disclosure failed to teach the successful inhibition of RNAi molecules with size ranges of less than approximately 550 nucleotides per targeting strand.

The instant rejection is hereby maintained for lacking possession of the broad genus of plants, eukaryotic cells and chimeric constructs claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 100-103, 109, 115-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flavell, Metzlaff et al, and Stam et al, the combination in view of Brown et al, Lusky et al for the reasons of record set forth in the Office action mailed 9-19-08 insofar as the claims are drawn to plants and eukaryotic cells comprising chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a DNA

region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes large strands of consecutive nucleotides having 100% sequence identity with at least 500 consecutive nucleotides of a nucleic acid of interest, and which antisense sequence includes at least 500 consecutive nucleotides having 100% sequence identity with said at least 500 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises any intronic sequence.

Applicant's arguments filed 11-5-09, and the declarations filed 5-7-08 and 3-19-09 have been fully considered but they are not fully persuasive.

Applicants and declarants argue that the instant invention would not have been obvious to one of skill in the art for several reasons. Applicants and declarants argue on the one hand that anyone of skill in the art would have realized that Applicants were in full possession of the very broad genus of plants, eukaryotic cells and constructs claimed, either prior to the time of filing (e.g. predating December 23, 1997) or at the time of filing the instant disclosure. On the other hand, declarants and Applicants argue that no one would have found the instant invention obvious at the time of filing the instant disclosure (i.e. after the filing of Fire priority documents, etc for USPN 6,506,559, or prior to December 23, 1997).

Applicants and declarants argue that the publications of Flavell, Metzlaff and Stam did not contemplate that double stranded RNA structures formed between antisense RNA and the sense mRNA could be a triggering agent in gene silencing.

Applicants and declarant argue that the hypotheses put forward during the mid-nineties were limited to four hypotheses: differences in methylation patterns or participating genes that interfere with transcription complex assembly, elevated competition between increased number of genes for non-diffusible sequence factors essential for transcription or translation, formation of aberrant duplexes of mRNAs and antisense RNA, and feedback inhibition due to accumulation of aberrantly high concentrations of a specific gene product in a transgenic plant, and that these four predominant hypotheses in the field essentially precluded the consideration of alternative hypotheses responsible for the cosuppression phenomena observed in plants and later in other eukaryotic cells.

Contrary to Applicants' and declarants' assertions, the discussions and investigations concerning the observed phenomena of gene suppression were not limited to four hypotheses, and the references of Flavell, Metzlaff and Stam repeatedly address the limitations of these existing hypotheses, and ponder the relationship between the existence of inverted repeats as well as the possible accumulation of sense/antisense constructs and the subsequence degradation of mRNA. See, e.g. Flavell on p. 3490: "Degraded RNA products from both genes were found in cosuppressed fruit, suggesting that RNA transcription is not inhibited and therefore loss of mature mRNA is due to posttranscriptional turnover." (last full paragraph on p. 3490). See also the first full paragraph on p. 3491 which dispels the role of methylation in target gene inhibition: "…suppression of activity was not correlated with methylation..." And the second full paragraph on p. 3491 provides motivation to study the role of self-complementary sequences in target gene inhibition: "Ninety base pairs of homology in

promoter sequences were sufficient to create a cosuppressed condition." Contrary to Applicants' assertions, investigators in the field in the mid-nineties were investigating the role of self-complementary constructs that formed aberrantly (and not excluding inverted repeats) in target gene inhibition. These self complementary constructs that resulted from the expression of inverted repeats were not limited to antisense-mRNA duplexes leading to mRNA degradation, and the presence and role of inverted repeats, particularly in observed flowering patterns in petunia, was questioned and discussed repeatedly throughout the decade preceding the Fire patent.

And, contrary to Applicants' assertions, the first paragraph on p. 3495 of Flavell invites further experimentation beyond the four proposed hypotheses:

> What is needed to evaluate the application of antisense RNA formation to the cause of down-regulation of homologous gene expression, in at least some examples of trans-inactivation by transgenes, is a much better understanding of how antisense RNA effects down-regulation of gene expression, measurements of antisense and sense RNA levels in the relevant cells and their nuclei before as well as after RNA degradation, and knowledge of the role of RNA-dependent RNA polymerase and of the ability of accumulated RNA products to feed back and interfere with transcription. It will also be important to discover the relationship between the mRNA turnover revealed by transgenes and endogenous posttranscriptional control systems that regulate mRNA turnover.

What's more, Stam repeatedly stresses the importance of the existence of inverted repeats and their role in gene inhibition: See figure 1 on p. 4 and the bridging paragraph of pages 3-4: "These T-DNAs can be arranged 'head-to-tail' as a direct repeat (DR), and 'head-to-head' or 'tail-to-tail' as an inverted repeat (IR). **Transgenes of T-DNAs that are organized as IRs often show low expression indicating that the genes are silenced to some degree**." (citations omitted, emphasis added). And on p.

8, last full paragraph: "There are at least two possibilities; the first is that a multicopy locus is prone to deliver the hypothetical aberrant RNA assumed to trigger the cytosolic RNA degradation machinery directly... One possibility is that it occurs as a result of ectopic DNA pairing between the transgene locus and the endogenous gene(s)... these transcripts may be intrinsically unstable and rapidly degraded, or may act as aberrant RNA causing the degradation of other homologous RNAs. Not all transgene loci may be able to pair ectopically with an endogenous gene. An essential property seems that they are repetitive. **Thus far, all the T-DNA loci that we have found to induce PTGS of *chs* contain two or more T-DNAs arranged as IRs**... There are no indications that the methylation status of the endogenous genes is changed." (citations omitted, emphasis added).

And in the first paragraph on p. 9, Stam again rules out methylation as a mechanism involved in target gene inhibition involving IRs:

> Observations with IRs and DRs in Drosophila, which lacks 5-methyl-cytidine in its DNA, indicate that repeats somehow interact with each other, leading to the formation of heterochromatin… By analyzing petunia transformants carrying CaMV-35S promoter-driven *chs* sense or antisense transgenes, Jorgensen et al. (1996) showed that the pattern of *chs* silencing in flowers correlated with the repetitiveness and organization of the transgenes in these plants. The pigmentation pattern caused by single-copy transgene inserts is mostly regular (junction type) whereas that by IRs is often complex and sometimes recognizable as the 'Cossack Dancer' pattern…"

Metzlaff also discusses the role of inverted repeats in target gene inhibition: On page 845, second full paragraph of the introduction: "Petunia plants are correlated with the number of transgenes and their arrangement in the genome." Metzlaff devotes

considerable thought to the relationship between self annealing sequences and resistance of those self annealing structures to degradation (see e.g. figure 5), as well as arguing that cosuppression is not merely due to the presence of high levels of chsA RNA (see first full paragraph on page. 850). The involvement of RNA-RNA pairing in RNA turnover is questioned: "Such complementarity may have been selected as a component of an RNA turnover control system by intra- or intermolecular RNA pairing." (second full paragraph from the end on page 852). And, reviewing Jorgensen's work, the role of inverted repeats in target gene suppression is questioned: "...whereas multiple copies of transgenes, and especially **inverted repeat** copies, enhance the probablitity of more extensive cosuppression and, in particular, cosuppression in leaves and stems." (second last paragraph of the discussion on p. 853) (emphasis added).

It is clear that the role of inverted repeats, and other double stranded RNA structures were pondered by those looking for underlying mechanisms of target gene suppression in eukaryotes, as illustrated by the teachings of Flavell, Stam and Metzlaff. It therefore would have been obvious to design, construct and test the ability of nucleic acid constructs comprising double stranded RNA for their ability to inhibit the expression of a known target gene in plants or in eukaryotic cells in vitro at the time of the instant invention.

For these reasons, the instant rejection is maintained.

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 100-103, 109, 115-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al in view of Brown et al,

Lusky et al and Schiedner et al, the combination in view of Baracchini et al insofar as the claims are drawn to plants, eukaryotic cells, and chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a DNA region encoding a region capable of forming an artificial hairpin RNA structure with a double stranded RNA stem by base pairing between regions with a sense and an antisense nucleotide sequence, which sense nucleotide sequence includes at least 20 consecutive nucleotides having 100% sequence identity with at least 20 consecutive nucleotides of a nucleic acid of interest, and which antisense sequence includes at least 20 consecutive nucleotides having 100% sequence identity with said at least 20 consecutive nucleotides of the sense sequence, and which chimeric DNA further comprises any intronic sequence for the reasons of record set forth in the Office action mailed 5-11-09.

Applicants, in their response filed 5-1-08, provided declarations describing experiments that were performed prior to December 23, 1997, the priority date of the Fire patent, USPN 6,506,559. The instant rejection, however, is directed to eukaryotic cells and plants comprising chimeric nucleic acids comprising RNAi constructs that comprise at least 20 nucleotides that are fully complementary and target a nucleic acid capable of being phenotypically expressed. Applicants also argue that they have provided proof of actual reduction to practice of the claimed invention prior to December 23, 1997, effectively removing the Fire patent (USPN 6,506,559) as prior art, and have asked why the declarations have been disregarded or deemed not appropriate in overcoming this rejection.

Applicants did not have support for the limitations claimed, particularly with respect to siRNA of at least 20 nucleotides in length per strand, for the reasons stated above in the written description rejection. It should perhaps also be pointed out at this juncture that Fire and Mello received the Nobel Prize in Physiology or Medicine in 2006 for their discovery of the fundamental mechanism for controlling the flow of genetic information (See accompanying Press Release from October of 2006). Pertinent parts of the Press Release are quoted here to illustrate that, while Applicants' can reasonably assert that they had support for what was specifically reduced to practice, as described below, comprising fully complementary pair constructs of at least 558 nucleotides in length, Applicants did not have possession of siRNA constructs comprising strands of at least 20 nucleotides in length. Nor was the mechanism of gene silencing using short siRNA molecules delineated until Fire and Mello had elucidated this silencing mechanism using short dsRNA molecules.

The press release describes the chronology of elucidation of siRNA gene silencing, for which Fire and Mello were awarded the Nobel Prize: "After a series of simple but elegant experiments, Fire and Mello deduced that double-stranded RNA can silence genes…"

> **Fire and Mello published their findings in the journal Nature on February 19, 1998. Their discovery clarified many confusing and contradictory experimental observations and revealed a natural mechanism for controlling the flow of genetic information.** This heralded the start of a new research field…

(emphasis added). What's more, the press release also explicitly states that "The components of the RNAi machinery were identified during the **following years**." Also

made clear in announcing the Nobel Prize was the fact that the mechanism causing petunias to change their color, had "remained enigmatic" until the work of Fire and Mello. It is therefore unclear how Applicants can state that they had proper support for the limitations instantly claimed, and by which they now seek to predate Fire's work, particularly using short siRNA molecules as instantly claimed.

The instant specification teaches fully complementary pair constructs for reducing the phenotypic expression of a transgenic Gus gene (of approximately **1580 base pairs**), and complementary pair constructs for reducing the phenotypic expression of the Δ12 desaturase target gene in *Arabidopsis* (of approximately **620 base pairs**) which complementary pair constructs additionally comprise the pyruvate orthophosphate dikinase 2 intron 2 from *Flaveria trinervia* (SEQ ID NO. 7) in forward or reverse orientation. The declarations filed 5-1-08 teach three expression constructs, one which comprises a double stranded hairpin of at least **750 base pairs** that comprises a sequence fully complementary to and targets the potato virus Y gene, and which expression construct further comprises intron 2 of pdkA, which was transformed into *Agrobacterium*, and a second and third double stranded construct of at least **558 base pairs** that targets and is fully complementary to the target GUS gene, and optionally comprise the Ubi-1 intron, which nucleic acid constructs were transformed into rice calli.

Fire et al (USPN 6,506,559) teach plant cells, plants and their seeds comprising a nucleic acid comprising a first and second DNA sequence which expresses in the plant cell a chimeric DNA comprising a promoter, operatively linked to a DNA region

which, when transcribed, yields and RNA molecule capable of forming a hairpin comprising two annealing RNA sequences which comprise a sense sequence sharing homology with consecutive nucleotides of a target nucleic acid of interest in the plant, and which further comprises a second, annealing RNA sequence comprising antisense sharing homology with the consecutive nucleotides of the sense strand that targets the nucleic acid of interest, and which chimeric DNA further comprises operably linked transcription termination and polyadenylation sequences. Fire teaches RNAi molecules comprising at least 25 nucleotides on the sense and antisense strands (see esp. claims 10, 15) (See also the abstract, col. 3-4, col. 5, line 47-col. 6, line 54, col. 7, line 42-col. 9, line 25, col. 11, line 37-col. 12, line 8, col. 17, line 20-24, col. 21, line 36-col. 22, line 4; col. 4, lines 41-61; col. 6, line 32-col. 9, line 48; col. 12, lines 46-col. 13, line 8; claims 1-12 and 21).

Fire et al (USPN 6,506,559) do not teach the RNAi expression constructs comprising an intervening intron sequence.

Brown et al (USPN 5,859,347) teach plant cells transformed with chimeric nucleic acid expression constructs expressing desired DNA sequences, and which expression constructs comprise expression elements including operably linked promoters and further comprising heterologous introns, which introns enhance stability and expression of the nucleic acid sequences in an expression construct (see col. 8, line 53-col. 9, line 17, examples 1-7 in cols. 10-18 and figures 8-27).

Lusky et al (USPN 6,350,575) teach expression constructs comprising antisense RNA and further comprising an intron as well as other expression elements including translation termination and polyadenylation signals (col. 6, line 15-col. 7, line 14).

Schiedner et al (Nature: Genetics, Vol. 18, pages 180-183, 1998) teach expression vectors comprising intronic sequences for enhancing vector stability (see esp. left col., p. 180).

Baracchini et al (USPN 5,801,154) teach the motivation and ability to target a gene of interest with a complementary sequence comprising at least 10 nucleobases (see e.g. claims 1, 12, 26, and 32).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to design and utilize chimeric constructs as instantly claimed to alter the expression of a target gene of known sequence, which gene is either endogenous or heterologous to a plant cell, which target gene is either stably integrated or extrachromosomal, comprising the introduction of nucleic acids comprising sense and complementary antisense sequences of the target gene, which are operably linked to a constitutive or heterologous promoter, and which are optionally expressed on separate or the same expression construct, and hybridize after their expression to the complementary sequences of each other to form a double stranded molecule, whereby a duplex is formed between the expressed sense and antisense fragments, because the efficiency of such methods of gene silencing have been previously taught Fire et al. One of ordinary skill in the art would have constructed RNAi constructs comprising 25 nucleobases on the sense and on the antisense strand, which are fully complementary

to the target nucleic acid of interest because Fire discloses RNAi molecules of this short size range. One of ordinary skill in the art would have expected the expressed double stranded RNA to target and inhibit the expression of corresponding target sequences of a target gene of known sequence, as taught previously by Fire et al.

One of ordinary skill in the art would have been motivated to include intronic sequences within the expression constructs for gene expression in plants because the use of intronic sequences for enhancing vector stability and hence enhance expression of a desired gene in cells had been taught previously by Brown et al and Schiedner et al. And Lusky et al and Fire also teach the incorporation of intronic sequences in expression constructs and it was well known in the art that the inclusion of introns enhances the expression of RNA in plants. One of ordinary skill in the art would have optionally placed the intronic sequences between the sense and antisense sequences in the chimeric construct originally taught by Fire et al because this is a design choice and additional, non-complementary sequences (e.g. intronic sequences) are included in the sense antisense constructs in order to allow for hairpin turns between complementary sequences. One of ordinary skill in the art would have expected that the intronic sequences, inserted at different places in the expression construct, would enhance expression of the chimeric constructs in plants and it would take routine experimentation to determine where in the construct the intron sequences would be inserted, as long and complementarity between the sense and antisense sequences was maintained for subsequent target gene inhibition. One of ordinary skill in the art would have been motivated to include the size range of 25 nucleobases for the targeting

strand of the double stranded gene silencing construct because Fire et al is the first to disclose RNAi constructs with targeting sequences to be in that size range (e.g. 25 nucleobases) and it would take routine experimentation to vary the range of sequences of the gene silencing constructs originally taught by Fire et al. Likewise, one of ordinary skill in the art would have expected that the range of 10-50 nucleobases, and sharing 100% homology would be effective in gene silencing, because Fire et al was the first to disclose RNAi constructs of this size range, Fire compared the advantages of various inhibitory oligonucleotides, including RNAi, antisense and ribozymes in their ability to inhibit target gene expression, and successful gene targeting has been routinely provided using antisense with a minimum length of 10 nucleobases (see also Baracchini et al). It would therefore take routine experimentation to alter the length of the target sequence as well as the homology required for successful gene silencing in plant cells relying on the teaching of Fire and Baraccini. One would have been motivated to express downstream and operatively linked sequences in DNA expression vectors to subsequently duplex RNA in a cell to target and inhibit target gene expression.

One of ordinary skill in the art would have been motivated to inhibit the expression of target genes by these expressed RNAi molecules, as described previously by Fire et al, for altering cellular phenotypes in order to study gene function, or to study the role of various target genes by comparing cellular processes in the absence or presence of these target genes expression, or to inhibit a deleterious pathogenic gene of an invading organism in a plant cell by inhibiting pathogenic target gene expression using this technique of gene silencing. One of ordinary skill in the art

would have expected that the inclusion of intronic sequences would enhance expression construct stability because the inclusion of intronic sequences in expression constructs was routine in the art, as evidence by the inclusion of intronic sequences in commercial and other published expression constructs, at the time the invention was made. One of ordinary skill in the art would have expected that the transformation of expression cassettes for target gene silencing in appropriate plant cells, whereby the concerted expression of both the sense and antisense fragments in appropriate target cells using appropriate promoters is obtained, leads to the formation of double stranded fragments directed to the target gene sequences in the transformed cells, and consequently interferes with the expression of the target gene, thereby producing inhibition of target gene expression, allowing a comparison of cellular phenotypes in the presence and absence of target gene inhibition, as taught previously by Fire et al.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 100-103, 109, 115-122 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22-29, 35-38 of copending Application No. 11/841,737. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets are drawn to plants and eukaryotic cells comprising chimeric DNA comprising an operable promoter, transcription termination and polyadenylation region, and further comprising a nucleic acid sequence encoding an RNAi molecule.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore, can be reached on (571) 272-2914. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
11-25-09

/Jane Zara/

Primary Examiner, Art Unit 1635